MEDICINAL PRODUCT PACKAGING

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of provisional U.S. patent application Serial No. 60/406,848, filed August 29, 2002.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to use of fluorinated plastic containers for medicinal products, particularly for highly potent medicinal preparations.

2. Description of the Related Art

Medicinal products must possess certain levels of stability and purity in order to be suitable for safe and efficacious administration to patients. Medicinal products are considered stable if the active ingredient can maintain its strength at the level specified on the label for the maximum anticipated shelf-life under given environmental conditions. A medicinal product is considered unstable when the active ingredient or excipients such as preservatives, flavoring agents, loses sufficient potency to adversely affect the safety or efficacy of the drug or falls outside labeled specifications. A typical example of relatively unstable medicinal agents is prostaglandin. The potency of a drug product may decline over time during storage due to various reasons, such as degradation of the active ingredient, reaction of the active ingredient with excepients or container materials, or leaching of the active ingredient through the container wall or absorption of the active ingredient into the container wall. In addition, many medicinal preparations contain preservatives, such as chlorobutanol, phenoxyethanol, methyl, and propyl parabens and benzalkonium chloride, as certain concentrations, which enable storage of the medicinal preparations for periods of time up to 24 months or more. The preservatives may permeate the container wall upon storage, reducing the concentration in the preparation, and as a result their preservative value is diminished. Similarly, the purity of a medicinal preparation may also change during storage due to leaching of chemical or chemicals into the drug preparation from the container materials, from the labels on the containers, or from the environment where the packaged medicinal product is stored. Thus, containers used for packaging medicinal preparations can significantly affect the stability and purity of the preparations.

Containers commonly used for medicinal products include glass containers, polypropylene containers, and polyethylene containers. Glass containers and polypropylene containers are said to be superior in maintaining stability of prostaglandin preparations (See U.S. Patent No. 6,235,781) and to have good permeability resistance to chlorobutanol (See U.S. Patent No. 5,799,837). However, because glass of containers are rigid and are not squeezable, they are not very suitable for medicinal preparations which need to be dispensed on a drop-by-drop basis. This type of containers, as well as non-permeable plastic containers, have been utilized in conjunction with an eye dropper type dispenser; however, this arrangement leads to non-sterile conditions due to exposure of the preparation to the atmosphere.

Typical user-friendly containers, or dispensers, or bottles, for medicinal preparations are formed from, for example, polyethylene, polypropylene (PP), polyethylene terpthalates (PET), which in most instances provide a suitable combination with a pharmaceutical preparation which results in a packaged medicinal product that is user-friendly for dispensing of the pharmaceutical preparation on a drop-by-drop basis.

Plastic containers, particularly containers made up of low density polyethylene however, have significant drawbacks. For example, polyethylene is permeable to many active agents or excipients. Thus, as an example, if the medicinal preparation includes chlorobutanol as a preservative, upon storage chlorobutanol permeates the container wall and evaporates, reducing the concentration in the preparation. Accordingly, its preservative value to the pharmaceutical preparation is diminished. This phenomenon occurs over a matter of days, depending on the storage temperature. If the chlorobutanol content in a medicinal preparation is reduced by about 40% due to loss through a container wall, the medicinal preparation may no longer meet preservative specifications. As hereinabove mentioned, this can occur in a matter of days if the container is formed from 100% polyethylene. Similarly, containers made up of LDPE may be permeable to label-related extractables such as adhesives, inks, varnishes, and curing agents. That is, when labels are placed on the outside of a LDPE container, extractable components from the label system may migrate from the label through the bottle wall and into the product matrix. The appearance of extractable components in the product matrix raises concern from several perspectives, including toxicity and patient exposure, and possible reduction of product stability due to

interaction with formulation ingredients. This is particular true when benzalkonium chloride is utilized as a preservative. In addition, U.S. Patent No. 6,235,781 discloses that prostaglandin preparations stored in PE container were not as stable as those stored in glass containers or polypropylene containers.

Therefore, there is a need for a packaged medicinal product and method for packaging medicinal preparations, which can increase the stability of the medicinal preparation, prevent the loss of an ingredient of the preparation, or prevent ingress of label related extractables or other impurity through the container walls.

SUMMARY OF INVENTION

In one aspect, the invention provides for packaged medicinal product having extended shelf-life comprising:

(a) a medicinal preparation; and

(b) a plastic container having a fluorinated barrier layer on a surface of the container body wall, wherein the body of the container is filled with the medicinal preparation.

The term "extended shelf-life" means the shelf-life of the medicinal preparation packaged in a container having a fluorinated barrier layer on a surface of the body wall is longer than that of the same medicinal preparation packaged in an identical plastic container except that the container does not have a fluorinated barrier layer.

In a particular embodiment, the invention provides for a packaged medicinal product having extended shelf-life comprising:

(a) a medicinal preparation; and

(b) a plastic container having a fluorinated barrier layer on a surface of the body wall, wherein the body of the container is filled with the medicinal preparation, wherein the medicinal preparation comprises a prostaglandin.

In another particular embodiment, the invention provides for a packaged medicinal product having extended shelf-life comprising:

(a) a medicinal preparation; and

(b) a plastic container having a fluorinated barrier layer on a surface of the body wall, wherein the body of the container is filled with the medicinal preparation, wherein the container is a small volume bottle.

In still another particular embodiment, the invention provides for a packaged medicinal product having extended shelf-life comprising:

(a) a medicinal preparation; and

(b) a plastic container having a fluorinated barrier layer on a surface of the body wall wherein the body of the container is fill with the medicinal preparation, wherein the packaged medicinal product is suitable for ophthalmic use, the medicinal preparation comprises a prostaglandin, and the plastic container is a small volume polyethylene container, typically 1 ml to 500 ml in volume.

In another aspect, the invention provides a method of packaging a medicinal preparation, said method comprising the steps of:

(a) providing a plastic container having a fluorinated barrier layer on a surface of its body wall; and

(b) filling the container body with the medicinal preparation.

In a particular embodiment, the invention provides for a method of packaging a medicinal preparation, said method comprising the steps of:

(a) providing a plastic container having a fluorinated barrier layer on a surface of its body wall; and

(b) filling the container with the medicinal preparation,

wherein the medicinal preparation comprises a prostaglandin.

In another particular embodiment, the invention provides for a method of packaging a medicinal preparation, said method comprising the steps of:

(a) providing a plastic container having a fluorinated barrier layer on a surface of its body wall; and

(b) filling the container with the medicinal preparation,

wherein the plastic container is a small volume bottle.

In still another particular embodiment, the invention provides for a method of packaging a medicinal preparation, said method comprising the steps of:

(a) providing a plastic container having a fluorinated barrier layer on a surface of its body wall; and

(b) filling the container with the medicinal preparation,

wherein the plastic container is a small volume polyethylene bottle and wherein the medicinal preparation comprises a prostaglandin.

In another aspect, the invention provides for a method of increasing the stability of a liquid medicinal preparation, said method comprising packaging the

liquid medicinal preparation in a plastic container having a fluorinated barrier layer on a surface of the container body wall.

As used herein, the term "increasing the stability" refers to maintaining the strength or potency of the preparation within given levels for a longer period of time, or maintaining the strength or potency of the preparation at higher levels within a given period of time, as compared with the preparation stored in an identical container except the container does not have a fluorinated barrier layer. Methods of determining the stability of a medicinal preparation is known in the art.

In a particular embodiment, the invention provides for a method of increasing the stability of a liquid medicinal preparation, said method comprising packaging the liquid medicinal preparation in a plastic container having a fluorinated barrier layer on a surface of the container body wall, wherein the liquid medicinal preparation comprises a prostaglandin.

In a particular embodiment, the invention provides for a method of increasing the stability of a liquid medicinal preparation, said method comprising packaging the liquid medicinal preparation in a plastic container having a fluorinated barrier layer on a surface of the container body wall, wherein the liquid medicinal preparation is for ophthalmic use.

In another particular embodiment, the invention provides for a method of increasing the stability of a liquid medicinal preparation for ophthalmic use, said method comprising packaging the liquid medicinal preparation in a plastic container having a fluorinated barrier layer on a surface of the container body wall, wherein the liquid medicinal preparation comprises a prostaglandin.

In another aspect, the invention provides for a method of preventing loss of an ingredient in a liquid medicinal preparation through the wall of a plastic container which contains the medicinal preparations, said method comprising packaging the medicinal preparation in a plastic container having a fluorinated barrier layer on a surface of its body wall. The term "preventing loss" of an ingredient refers to reducing the loss of the ingredient to any extent. Depending on the specific ingredient of interest, the loss may be slightly reduced or may be completely prevented. The ingredient whose loss is desired to be prevented with the method of the invention can be an active ingredient or an excipient in the preparation.

This method is particularly advantageous for a medicinal preparation which comprises a highly potent active ingredient, such as a prostaglandin.

In a particular embodiment, the invention provides for a method of preventing loss of an ingredient in a liquid medicinal preparation through the wall of a plastic container which contains the medicinal preparations, said method comprising packaging the medicinal preparation in a plastic container having a fluorinated barrier layer on a surface of its body wall, wherein the active ingredient is a prostaglandin.

In another aspect, the invention provides a method of reducing transfer of an impurity into a liquid medicinal preparation upon storage, comprising packaging the liquid medicinal preparation in a plastic container said container having a fluorinated barrier layer on a surface of the container body wall. The term "impurity" as used herein refers to a component in a medicinal preparation packaged in a container which component is not a desired ingredient in the preparation and is introduced into the preparation from or through the wall of the container. An impurity may have its origin in the container wall materials, or, if a label is attached to the outside of the container, in label-related materials such as adhesives, inks, varnishes, and curing agents, or in the environment wherein the packaged preparation is stored, such as secondary packing materials.

DETAILED DESCRIPTION OF THE INVENTION

A. Medicinal preparations.

As used herein, the term "medicinal preparation" refers to matter of compositions whose biological, physiological, pharmacological, or chemical activities are beneficial for animals or humans in normal or pathological conditions, such as diagnosis, prognosis, treatment, prophylaxis, therapy, or for animal production.

Any suitable medicinal preparation may be incorporated into the present invention. Thus, for the present invention, the medicinal preparations are not limited by their specific applications, physical forms, formulations, or specific dosage forms. For example, the preparations can be in the form of power, capsule, tablet, or liquid and any other forms. Liquid preparations, however, are more advantageously suitable for incorporation into the present invention, and can be a suspension, solution, emulsion, or in other liquid form, or can be aqueous or non-aqueous.

The medicinal preparations suitable for incorporation into the present invention are not limited by their usage or indication, or the potency, physical,

chemical, pharmacological, or biological nature of their ingredients. It is more advantageous, however, that preparation comprises a highly potent active ingredient. Examples of highly potent active ingredient include, but not limited to, anticancer agents; anti-HIV agents; anti-toxins; hormones; steroids; potent pain killers etc.

A specific example of highly potent active ingredient is prostaglandin. The terms "prostaglandin" and "PG" are generally used to describe a class of compounds which are analogues and derivatives of prostanoic acid. PG's may be further classified, for example, according to their 5-membered ring structure, using a letter designation; PG's of A-J series are known. PG's may be further classified based on the number of unsaturated bonds on the side chain, e.g., PG1 's (13,14-unsaturated), PG2 's (13,14- and 5,6-unsaturated), and PG3 's (13,14-,5,6- and 17,18-unsaturated). See U.S. Pat. No. 5,631,287. Various prostaglandins and prostaglandin preparations are also disclosed in US patent No. 6,235,781. The prostaglandins which may be utilized in the present invention include all pharmaceutically acceptable prostaglandins, their derivatives and analogues, and their pharmaceutically acceptable esters and salts. Such prostaglandins include the natural compounds: PGE1, PGE2, PGE3, PGF1α., PGF2α., PGF3α, PGD2 and PGI2 (prostacyclin), as well as analogues and derivatives of these compounds which have similar biological activities of either greater or lesser potencies. Analogues of the natural prostaglandins include but are not limited to: alkyl substitutions (e.g., 15-methyl or 16,16-dimethyl), which confer enhanced or sustained potency by reducing biological metabolism or alter selectivity of action; saturation (e.g., 13,14-dihydro) or unsaturation (e.g., 2,3-didehydro, 13,14-didehydro), which confer sustained potency by reducing biological metabolism or alter selectivity of action; deletions or replacements (e.g., 11-deoxy, 9-deoxo-9-methylene), chloro (or halogen) for oxygen (e.g., 9beta.-chloro), oxygen for carbon (e.g., 3-oxa), lower alkyl for oxygen (e.g., 9-methyl), hydrogen for oxygen (e.g., 1-CH2 OH,1-CH2 OAcyl) which enhance chemical stability and/or selectivity of action; and .omega.-chain modifications (e.g., 18,19,20-trinor-17-phenyl, 17,18,19,20-tetranor-16-phenoxy), which enhance selectivity of action and reduce biological metabolism. Derivatives of these prostaglandins include all pharmaceutically acceptable salts and esters, which may be attached to the 1-carboxyl group or any of the hydroxyl groups of the prostaglandin by use of the corresponding alcohol or organic acid reagent, as appropriate. It should be understood that the terms "analogues" and "derivatives"

include compounds that exhibit functional and physical responses similar to those of prostaglandins per se.

Specific examples medicinal preparations comprising a prostaglandin suitable for the present invention include Xalatan ® (Pharmacia &Upjohn) or Rescula ® (Novartis Ophthalmics). Xalatan ® is an aqueous ophthalmic solution of latanoprost, which contains 50 micrograms/mL of latanoprost, 0.02% benzalkonium chloride as a preservative, and inactive ingredients such as sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous and water for injection. Rescula® is an aqueous ophthalmic solution of unoprostone isopropyl, which contains 1.5 mg/mL of unoprostone isopropyl, 0.015% benzalkonium chloride as a preservative and inactive ingredients such as mannitol, polysorbate 80, edetate disodium, sodium hydroxide or hydrochloric acid (to adjust pH), and water for injection.

One particular example where such a situation may arise is in the packaging of ophthalmic preparations which are packaged in a wide variety of plastic bottles (small and large volume; polypropylene or PP, low density polyethylene or LDPE and high density polyethylene or HDPE etc.). Some ophthalmic formulations contain potent therapeutic agents (e.g. prostaglandins like latanoprost in Xalatan ® or travoprost in Travatan ®) and a large majority of the formulations also contain preservatives (e.g. chlorobutanol, methyl- and propyl-parabens, benzalkonium chloride or BAC etc.) and stabilizers (surfactants such as polysorbate 80, antioxidants etc.). Among these, prostaglanidns, chlorobutanol and the parabens are known to be prone to sorptive losses by the container.

B. Containers.

1. Container Materials.

The container for use with the invention can be made of any suitable thermoplastic materials. Examples of such materials include, but not limited to, polymers and copolymers of polystyrene, polyacrylonitrile, polyvinyl chloride, polyethylene terepthalates (PET) and PET copolyetster (PETG), polycarbonate, polymethacrylates, and particularly polyolefins. Polyolefins include, for example, polyethylene, polypropylene, polybutenes, polyisoprenes and polypentenes and copolymers and mixtures thereof.

An example of particular suitable plastic materials is polyethylene or a blend of polyethylene and one or more other materials. Polyethylene is commonly divided into classes based on its density. Classes commonly used include low-density polyethylene (LDPE), medium-density polyethylene (MDPE) and high-density polyethylene (HDPE). This list of classifications should not be considered as a standard or a complete list of classifications. Given these rather loose classifications, polymer characteristics vary among multiple producers of a given class of polyethylene, or among multiple grades of a given class by one producer. Furthermore, what one producer terms LDPE might be considered MDPE by another producer. Despite these variations, some generalizations can be made. Table 1 lists typical values for some physical, mechanical and thermal properties of LDPE as used herein.

Table 1. Typical Properties of Low Density Polyethylene

Property	Value	Range / Comments
Density, g/cc	0.91	0.910-0.925 g/cc
Hardness, Shore D	44	41-46 Shore D
Tensile Strength, Yield, Mpa	10	4-16 MPa; ASTM D638
Tensile Strength, Ultimate, Mpa	25	7-40 MPa
Modulus of Elasticity, Gpa	0.2	0.07-0.3 GPa; In Tension; ASTM D638
Flexural Modulus, Gpa	0.4	0-0.7 GPa; ASTM D790
Coefficient of Thermal Expansion, linear 20°C, Tm/m-°C	30	20-40 Tm/m°1C; ASTM D696
Melting Point, °C	115	

Table 2 lists typical values for some physical, mechanical and thermal properties of MDPE as used herein.

Table 2. Typical Properties of Medium Density Polyethylene

Property	Value	Range / Comments
Density, g/cc	0.93	0.926-0.940 g/cc
Hardness, Shore D	55	50-60 Shore D
Tensile Strength, Yield, Mpa	16	8-24 MPa; ASTM D638
Tensile Strength, Ultimate, Mpa	25	8.3-45 MPa
Modulus of Elasticity, Gpa	0.3	0.14-0.41 GPa; In Tension; ASTM D638
Flexural Modulus, Gpa	0.7	ASTM D790
Coefficient of Thermal Expansion, linear 20°C, Tm/m-°C	27	ASTM D696
Melting Point, °C	125	

Table 3 lists typical values for some physical, mechanical and thermal properties of HDPE as used herein. HDPE may further include higher density polyethylenes beyond the density range of 0.941-0.97 g/cc listed here as typical.

Table 3. Typical Properties of High Density Polyethylene

Property	Value	Range / Comments
Density, g/cc	0.95	0.941-0.97 g/cc
Hardness, Shore D	65	60-70 Shore D
Tensile Strength, Yield, MPa	30	20-40 MPa; ASTM D638
Tensile Strength, Ultimate, MPa	50	20-70 MPa
Modulus of Elasticity, GPa	0.8	0.4-1.2 GPa; In Tension; ASTM D638
Flexural Modulus, GPa	1.4	0.7-2 GPa; ASTM D790
Coefficient of Thermal Expansion, linear 201C, Tm/m-°C	22	ASTM D696
Melting Point, °C	130	

The container suitable for the invention can be made of polyethylene of any density, made of a blend of polyethylene of various densities, or made of a blend of polyethylene with other materials. For medicinal preparations that are desirably packaged in squeezable containers, particularly ophthalmic medications, however, it is more advantageous that the container of the invention is made of material comprising LDPE. Depending on the desired level of squeezability of the container, the relative content of LDPE in the container materials can be adjusted accordingly. Generally, containers made of LDPE is more readily squeezable than container made of MDPE or HDPE. Similarly, containers made of materials containing relatively high content of LDPE is more readily squeezable than container made of materials containing relatively low content of LDPE.

2. Shape, Style, and/or Size of the Container.

The shape, style, and/or size of containers for use with the prevent invention is unimportant. For example, the container can be bottle, a vial, or syringe. For use with liquid preparations containing prostaglandin or other highly potent ingredient, the container is preferably a "small volume" bottle. As used herein, the term "small volume" bottle shall mean a bottle of a size sufficient to hold a quantity of liquid medicine sufficient for 1-3 topical doses per day over 1-2 months, generally about 20 mL or less. For example, small volume containers include 5 mL-, 10 mL- and 15 mL-sized bottles adapted for topically administering eye drops. Small volume bottles made from LDPE are easier to squeeze than larger bottles, and oval bottles are easier to squeeze than round bottles. Accordingly, the liquid preparations adapted for topical ophthalmic administration are preferably packaged in oval, LDPE bottles.

3. Fluorinated Barrier Layer.

The container suitable for the invention has a fluorinated barrier layer on a surface of the body wall. The fluorinated barrier layer can be on the inside surface, outside surface, or both inside and outside surfaces of the container body wall. It is preferred that the container has a fluorinated barrier layer on the inside surface of the container body wall, which is the surface that is in contact with the medicinal preparation.

The fluorinated barrier layer can cover an entire surface of the container body wall, or it can cover only a portion or portions of a surface of the body wall. It is preferred that the fluorinated barrier layer covers an entire surface of the container

body wall, and it is particularly preferred that fluorinated barrier layer covers the entire inside surface of the container body wall. Generally, the fluorinated barrier layer should display no discontinuities to provide the best barrier. Minor gaps might not prove intolerable, depending upon the conditions and levels of desired barrier property.

The fluorinated barrier layer on the container body wall can be of any thickness. Generally, the barrier property of the fluorinated barrier layer increases as the thickness of fluorinated barrier layer increases. Thus depending on level of desired barrier property, the thickness of the fluorinated barrier layer can be varied over a wide range. The barrier layer can be as thin as a monomolecular layer of fluorination on a surface of the container wall. For most applications, however, the thickness of the fluorinated barrier layer generally lies in the range of from about 0.1 mm to 0.5 mm, typically about 0.2 mm. The fluorinated barrier layer does not necessarily involve the formation of a separate identifiable layer of the barrier compound. Rather, the requisite barrier layer of fluorinated polyolefin proceeds through the formation of a continuous film of the fluorinated polyolefin.

The fluorinated barrier layer on a surface of a container suitable for the present invention can be prepared using various methods known in the art, one of such method being fluorination process. Fluorination of polyethylene and other polymeric materials in the production of containers is well known; see for example, U.S. Pat. Nos. 4,142,032, 4,404,256; 4,264,750; 4,593,050, 4,701,290, 4,830,810; 4,617,077; 4,869,859, 5,073,231, 5,691,016.

There are two processes commonly commercially used to produce fluorinated containers: the "in-line" and "post molding" process. In the In-Line process, fluorine is injected inside the container and allowed to react while the container remains clamped in the mold of the blow-molding machine. This treats only the inside surface of the container.

In the Post-Mold fluorination process, manufactured containers are loaded into tightly sealed treatment chambers or reactors where air is pumped out and fluorine is introduced and allowed to react with the containers being treated. The reaction takes place under controlled conditions and allows a range of reproducible fluorination levels to be readily achieved. Containers of different styles and sizes can be mixed in a given load, as can containers of

different colors. The Post-Mold fluorination process treats both the inside and the outside surfaces of containers which yields a double layer of protection and potential for greater barrier than the In-Line process can produce. Post-mold fluorination is the preferred process. In certain instances it may be required to subject containers to two or more fluorination cycles to get adequate barrier properties.

Polyethylene containers of various sizes suitable for fluorination are commercially available. Examples of such a plastic containers include small spray-pump type bottles and LDPE dropper bottles of various sizes, such 5 mL, 7.5 mL, 10 mL, or 30 m, marketed by Prime Packaging.

An experiment was performed that demonstrated the usefulness of the invention described here. The experiment and the results provided are simply an example and should not be considered limiting the invention or the claims in any way merely because of its inclusion here.

MATERIALS AND METHODS SECTION

Polypropylene bottles (dropper-type) were obtained from Owens-Brockway, Illinois (capacity 5 ml). Some of the bottles were sent to a company called Fluoro-Seal (Columbus, Ohio) where they were treated for fluorine-coating under a proprietary method. After the bottles were 'fluorosealed' (done at 'level 5') they were washed in dilute soap solution rinsed several times in de-ionized water and dried before use. The bottles were then filled with 3 ml of a chlorobutanol and paraben test solution (Table 4). Control samples of untreated polypropylene bottles filled with the same solution were also prepared. All samples were prepared in duplicate and put up on accelerated stability at 56°C. Before putting on stability, '0' time-point samples from all bottles were collected and the bottles were weighed. Concentration of cholorobutanol and methyl- and propyl parabens was determined by an HPLC method. Samples were taken at 1 wk, 2wk and 4 wks by expelling ~50-100mcg droplets into tared vials. Bottles were weighed before and after sampling, before returning to condition. The following terms are used in Table 4, below. PP means polypropylene (untreated) . PP-FL or PP-FL5 means fluorinated polypropylene at service provider's specified level of '5'. LDPE is low density polyethylene (untreated). LDPE-FL5 means low density polyethylene fluorinated at service provider's specified level of '5'. Duplicate samples were measured.

The results are presented in Table 4, below.

CHLOROBUTANOL/PARABEN TEST
SOLN. 1
CHLOROBUTANOL 56C Data

TIME OF STORAGE	PP-1	PP-2	FL-5 PP-1	FL-5PP-2
0	**5.13**	**5.1**	5.23	5.1
1	**2.37**	**1.97**	4.01	3.99
2	**1.85**	**1.26**	3.72	3.74
4	**1.36**	**0.91**	3.42	3.59

Conc. In mg/ml

PROPYLPARABEN 56C Data

TIME OF STORAGE (weeks)	PP-1	PP-2	FL-5 PP-1	FL-5PP-2
0	103	103	**104**	**102**
1	86.2	86.9	**95.3**	**95.3**
2	82.5	77.8	**96.6**	**96.6**
4	69.5	65.1	**89.3**	**94.6**

Conc. In mcg/ml